DETAILED ACTION

1. The amendment filed August 16, 2011, is acknowledged and has been entered. Claim 4 has been cancelled. Claims 1, 2, 5, 6 and 18-20 have been amended. Claims 28-32 have been added.

2. The species election filed January 25, 2012, is acknowledged and has been entered.

Applicant has elected the compound which is an antineoplastic agent as the elected species further administered in the claimed methods. Applicant has submitted that claims 28 and 30-32 read on the elected species. However, claim 30 recites that the compound of claim 28 acts on the malignant tumorous disease via T cells in the human patient and the specification at page 13 sets forth that the methods of the invention include "co-administration protocols with other compounds, e.g., bispecific antibody constructs, targeted toxins or other compounds, which act via T cells or other compounds such as antineoplastic agents which act via other mechanisms". Accordingly, as the specification sets forth that antineoplastic agents act via mechanisms other than T cells, claim 30 does not read on the elected species and has been withdrawn for this reason.

Because applicant did not distinctly and specifically point out the supposed errors in the species requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

3. Claims 1-3, 5-11, 18-20, 23-25 and 28-32 are pending in the application. Claims 10, 11, 25 and 29-30 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention or a non-elected species of invention, there being no allowable generic or linking claim. Applicant elected without traverse in the reply filed October 14, 2008.

4. Claims 1-3, 5-9, 18-20, 23, 24, 28 and 31-32 are under examination. The

elected invention is drawn to a method of treating colon cancer in a human patient by administering to said patient a human immunoglobulin specifically binding to the human EpCAM antigen, said immunoglobulin exhibiting a serum half-life of at least 15 days, said method comprising the step of administering said immunoglobulin no more frequently than once every week and the elected species further administered in the claimed methods is an antineoplastic agent.

Grounds of Objection and Rejection Withdrawn

5. Unless specifically reiterated below, Applicant's amendment and/or arguments filed August 16, 2011, have obviated or rendered moot the grounds of objection and rejection set forth in the previous Office action mailed March 16, 2011. Notably, Applicant's amendment of the claims has rendered moot the previous 103(a) rejection because the claims now recite administering the human antibody once every three weeks instead of administering the human antibody once every one to two weeks. However, in order to promote compact prosecution, Applicant's arguments and Dr. Kaubitzsch's 1.132 declaration will be addressed in the new 103(a) rejection set forth below.

New Grounds of Rejection

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.

2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

7. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

8. Claims 1-3, 5-9, 18-20, 23 and 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kufer et al (WO 98/46645 A2, 1998, of record), in view of Raum et al (Can. Immunol. Immunother., 50:141-150, 2001, of record), in view of Naundorf et al (Int. J. Can. 100:101-110, 2002, of record), in view of Korman et al (US 20020086014 A1, 2002, of record), in view of Saint-Remy et al (US 20030175268 A1, 2003), in view of Schwab et al (US 20040033543 A1, 2004) in view of Wolf et al (DDT., 7(5):S25-S27, 2002, of record) and in view of Leyland-Jones (J. Clin. Onc., 221(21):3965-3971, 2003, of record).

As drawn to the elected invention and as currently amended, the claims are herein drawn to methods of treating colon cancer with EpCAM expression elevated relative to healthy colon tissue in a human patient comprising administering to said patient a human antibody comprising a heavy chain with the amino acid sequence of SEQ ID NO: 1 and a light chain with the amino acid sequence of SEQ ID NO: 2, wherein the antibody specifically binds to the human EpCAM antigen, said method comprising the step of administering said human antibody once every three weeks.

Dependent claims are further drawn to such methods, further comprising: (a) determining, after a period of at least one week following a respective last administration of said antibody but prior to a respective next administration of said antibody, the serum level of said antibody still present in the blood of said patient, thereby obtaining an intermediate serum level value for said antibody; (b) comparing said intermediate serum level value for said antibody with a predetermined serum trough level value for said antibody; and (c) effecting the respective next administration if the intermediate serum level value for said antibody is no more than 15%, preferably 10%, most preferably 5% above the serum trough level value or further comprising repeating steps (a) and (b) prior to step (c), or wherein the magnitude of the dose of said human antibody administered is set such that, at the end of the intervening time between two respective administrations, the amount of said human antibody persisting in the serum does not drop below the predetermined serum trough level, wherein the administered dose of said human antibody remains unchanged from one administration to the next, wherein the magnitude of the initial and all subsequent doses is determined by pharmacokinetic simulation and wherein said administering is intravenous, intraperitoneal, subcutaneous, intramuscular, topical or intradermal administration.

Kufer et al teach a human IgG1 antibody designated "H79" which comprises a heavy chain with the amino acid sequence of SEQ ID NO: 1 and a light chain with the amino acid sequence of SEQ ID NO: 2. This antibody has also been designated HD69, MT201 and adecatumumab in the art (see footnote[1]-also for the sake of clarity this antibody will be referred to the MT201 antibody in the rest of the action). Furthermore, as acknowledged by Applicant in the response filed May 26, 2009 at page 10, the MT201 antibody comprises the amino acid sequence of SEQ ID NO: 1 and the amino

[1]The antibody comprising a heavy chain with the amino acid sequence of SEQ ID NO: 1 and a light chain with the amino acid sequence of SEQ ID NO: 2 appears to have been designated H79, HD69, MT201 and adecatumumab in the art. For example, Oberneder (of record) evidences that adecutmamab has also been designated MT201 (see abstract). Then Naundorf (of record) teaches that the MT201 antibody has also been designated HD69 (see page 102, left column). Finally, Kufer et al (of record) teach a antibody designated H79 that comprises a 4.5 heavy chain and a k8 light chain with heavy chain and light chain variable sequences set forth in figures 6 and 7 that are these sequences are present in SEQ ID NO: 1 and a light chain with the amino acid sequence of SEQ ID NO: 2 (see also page 35-37), while Raum et al teach the same sequences for the antibody designated HD69 (see Figure 1 and page 145).

acid sequence of SEQ ID NO: 2. Kufer et al also teach methods of administering said MT201 antibody to human patients with a cancer expressing EpCAM by intravenous, intraperitoneal, subcutaneous, intramuscular, topical or intradermal administration and that the antibody is suitable for repeated in vivo administration at a suitable dose (see entire document, e.g., abstract and pages 1, 2, 12, 15 and 17). While Kufer et al does not point to particular cancers in the genus of cancers to be treated, Kufer et al teaches that a murine monoclonal antibody 17-1A that binds human EpCAM was known to treat human colon or colorectal cancer as well as teaching that the MT201 antibody can bind to human colon carcinoma cells (see e.g., 2 and 23). Furthermore, this deficiency is made up for in the teachings of Naundorf et al and Raum et al.

Naundorf et al teach that the MT201 antibody is effective in treating a mouse xenograft model of colon cancer derived from the human carcinoma cell line HT-29 that expresses EpCAM (see entire document, e.g., abstract). Raum et al teach that the murine monoclonal antibody designated 17-1A that binds human EpCAM was known to treat human colon or colorectal cancer, and that the H79 antibody, now designated HD69 in this reference (see footnote), closely resembles the binding properties of the murine antibody, but that this antibody displays better cytotoxic effector functions as compared to the 17-1A antibody (see entire document, e.g., abstract, Table 1 and 146, right column to 147, left column).

Furthermore, while Kufer et al teaches the MT201 antibody can be used in treatment protocols with repeated in vivo administration of the antibody, Kufer et al, Raum et al and Naundorf et al do not expressly teach antibody administration every three weeks or the other dosing schedules of delivery. These deficiencies are made up for in the teachings of Korman et al, Saint-Remy et al, Schwab et al, Wolf et al and Leyland-Jones.

Korman et al teach methods of administering human antibodies to patients and that dosage regimens should be adjusted to provide the desired response and that dosage regimens can change over time by the exigencies of the therapeutic situation and that selected dosage regimens depend upon a variety of pharmacokinetic factors including the activity of the particular compositions of the present invention employed, or

the ester, salt or amide thereof, the route of administration, the time of administration, the rate of excretion of the particular compound being employed, the duration of the treatment, other drugs, compounds and/or materials used in combination with the particular compositions employed, the age, sex, weight, condition, general health and prior medical history of the patient being treated, and dosages need to be titrated to optimize safety and efficacy. Korman also teach that human antibodies have a long half-life (see entire document e.g., pages 19 and 20).

Saint-Remy et al teach that fully human IgG antibodies have a half-life of about three weeks in humans (see entire document, e.g., pages 3, 4 and 6).

Schwab et al et al teach administering fully human antibodies every three weeks in treating human patients (see entire document, e.g., page 6).

Wolf et al teach that the MT201 antibody has a half-life of several weeks and is in clinical Phase I/II trials in humans for treating cancers that express EpCAM (see entire document, e.g., pages s25 and S27).

Leyland-Jones (see entire document) teach that antibody pharmacokinetic simulations used to establish dose schedules for therapeutic antibodies, predetermined serum trough levels and dose schedules for the respective next administration to maintain a minimum serum trough level of antibody are known in the art.

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to administer to human colon cancer patients the human MT201 antibody that specifically binds to human EpCAM once every three weeks and wherein the methods further comprise the various dosing schedules as set forth in the claims. Notably, one of skill in the art would have been motivated to administer such antibodies to humans with colon cancer every three weeks because EpCAM antibodies were known in the art to be effective at targeting and killing colon cancer cells which would treat the colon cancer expressing EpCAM, the MT201 antibody was known to target and kill colon cancer cells to treat human colon cancer in a mouse model and the human antibody was known to have a half-life of several weeks.

In this case, while the prior art MT201 antibody was at a relatively new stage of development so that further clinical data was not yet available, it is clear that the prior

art taught how to obtain clinical data as evidenced by the references and one of skill in the art would have motivated to obtain that data in order to treat humans. Furthermore, the MT201 antibody was in clinical trials and was known to have a half-life of several weeks, human antibodies with three week half-lives were known and human antibodies were known to be administered at three week intervals. Accordingly, it is submitted that administering the antibody every three weeks was *prima facie* obvious because the art taught methods where the frequency of antibody administration correlates with the half-life of the antibody (see e.g., Leyland-Jones that estimated a half-life of 18-27 days for the particular antibody administered in their studies and administered that antibody every 21 days) and because Saint-Remy et al teach that fully human IgG antibodies have a half-life about three weeks in humans and Schwab et al teach administering fully human antibodies every three weeks.

Furthermore, as evidenced by Korman et al, many pharmacokinetic factors affect the dosage regimen for any particular patient, dosage regimens should be adjusted to provide the desired response and dosage regimens can change over time by the exigencies of the therapeutic situation and Leyland-Jones further evidence that antibody pharmacokinetic simulations used to establish dose schedules for therapeutic antibodies are known in the art, so it is further submitted that absent a showing of unexpected results commensurate in scope with the claimed methods that the claimed methods of colon cancer treatment would be considered to be obvious by one of ordinary skill in the art in treating colon cancer patients with anti-cancer antibodies as they would have predictably expected the claimed antibody to be effective to some extent to treat colon cancer when administered at some dose every three weeks based on its half-life and using antibody pharmacokinetic simulations to establish dose schedules. Notably, the Naundorf et al and Raum et al references evidence that multiple EPCAM antibodies were known in the art using different dosing schedules, so it is apparent that depending on the patient and the amount administered many different administration time frames including three week intervals would be effective when administering the MT201 antibody.

Notably, the MT201 antibody was known in the art as a therapeutic antibody which can treat colon cancer, i.e., the antibody was known in the art as a variable which achieves a recognized result and as set forth in MPEP 2144.05: "A particular parameter must first be recognized as a result-effective variable, i.e., a variable which achieves a recognized result, before the determination of the optimum or workable ranges of said variable might be characterized as routine experimentation. In re Antonie, 559 F.2d 618, 195 USPQ 6 (CCPA 1977).

In this case, the prior art of Kufer et al, Raum et al, Naundorf et al and Wolf et al evidence that the human MT201 antibody was cytotoxic to human colon cancer cells expressing EpCAM, and that the antibody had advantageous properties such as longer serum half-life, improved cytotoxic effector functions and reduced immunogenicity as compared to a murine antibody that binds the human EpCAM antigen which can treat colon cancer patients, so one of skill in the art would have clearly recognized that the MT201 antibody would treat colon cancer and that the MT201 antibody was a result effective variable for treating colon cancer which could have workable or optimum dosing schedules determined by art-known pharmacokinetic techniques so that the antibody could be predictably used in methods of treating colon cancer patients expressing the human EpCAM antigen by administering the antibody every three weeks. Therefore, one of skill in the art clearly would have been motivated to establish a dose, schedule, and route of delivery that is both safe and effective, so as achieve a working therapeutic effect in treating colon cancer patients.

Secondly, as the half-life of the MT201 human antibody was known to be several weeks, human antibodies were known to have long half-lives of about three weeks and human antibodies were known to be administered at three week intervals and because one of skill in the art would have been motivated to monitor the half-life and other pharmacokinetic parameters in human patients undergoing treatment so as to provide effective colon cancer treatment, it is also submitted that one of skill in the art would have recognized that administering the antibody every three weeks would be a workable dosage schedule, i.e. a dosage schedule that would treat the colon cancer, as the schedule corresponds to the half-life of the antibody and the dose ***amount*** could be

adjusted so that an amount that was effective to treat colon cancer could be administered every three weeks to maintain an effective serum amount of the MT201 antibody in the patient due to its long half-life. Notably, the claimed methods only recite that treatment occurs. There is no requirement on the amount of treatment or the kind of treatment that needs to occur and there is no evidence of record that reasonably establishes that one of skill in the art would not have considered that administering the antibody every three weeks would be effective to treat colon cancer to some extent. In this case, in view of the evidence as a whole that the antibody had a long half-life and was effective to kill colon cancer cells, it is submitted that one of skill in the art would have reasonably expected success in treating colon cancer by administering the antibody every three weeks or by the other claimed parameters and one of skill in the art would have considered the claimed dosing parameters to be obvious variants of the prior art methods of treating colon cancer with the MT201 antibody as they would have been motivated to administer the antibody every three weeks based on its half-life of several weeks. Finally, it is further submitted that one of skill in the art would have been motivated to administer the antibody every three weeks rather than shorter intervals as patients would only need to come in for treatment every three weeks and because some side effects (such as injection site infections) would be reduced based on less frequent administration.

Furthermore, while this is a new ground of rejection, in the interests of compact prosecution, it is noted that Dr. Kaubitzsch has provided a declaration under 37 CFR 1.132 with statements regarding administering the adecatumumab antibody (the same antibody as instantly claimed and disclosed in the prior art-see footnote 1) to breast cancer patients in combination with docetaxel.

Notably, Dr. Kaubitzsch sets forth that when administering adecatumumab to breast cancer patients in combination with docetaxel that there is an unexpected advantage of administering the antibody every three weeks as opposed to every week (see points 2-10 of the declaration).

In response, while the evidence and Dr. Kaubitzsch's declaration have been considered as a whole, the declaration was not found persuasive with respect to the

rejection set forth above. Notably, while Dr. Kaubitzsch's declaration is directed to treating breast cancer with adecatumumab in combination with docetaxel, the elected invention is treating colon cancer and does not require administering docetaxel. Furthermore, the declaration provides no evidence or scientific reasoning that administering adecatumumab alone to colon cancer patients every three weeks has any unexpected advantage.

Therefore, the supplied declaration has not been found persuasive because the evidence provided is not commensurate in scope with the claimed methods. Notably, as set forth in MPEP 716.02 (d), "the "objective evidence of nonobviousness must be commensurate in scope with the claims which the evidence is offered to support." In other words, the showing of unexpected results must be reviewed to see if the results occur over the entire claimed range. *In re Clemens*, 622 F.2d 1029, 1036, 206 USPQ 289, 296 (CCPA 1980)".

Additionally, Applicant argues in the response filed August 16, 2011, that the claims as now presented recite methods of administering the antibody once every three weeks that are neither taught nor suggested by the previously cited prior art.

In response, while the amendment of the claims to recite administering the antibody every three weeks obviates the previous grounds of rejection, upon further consideration and search of the newly amended claims, a new ground of rejection is set forth above.

Therefore, after considering the record as a whole, the claimed methods were *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

9. Claims 28 and 31-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kufer et al (WO 98/46645 A2, 1998, of record), in view of Raum et al (Can. Immunol. Immunother., 50:141-150, 2001, of record), in view of Naundorf et al (Int. J. Can. 100:101-110, 2002, of record), in view of Korman et al (US 20020086014 A1, 2002), in view of Saint-Remy et al (US 20030175268 A1, 2003, in view of Schwab et al (US 20040033543 A1, 2004) in view of Wolf et al (DDT., 7(5):S25-S27, 2002, of record)

and in view of Leyland-Jones (J. Clin. Onc., 221(21):3965-3971, 2003, of record), as applied to Claims 1-9, 18-20, 23 and 24 above, and further in view of Rao et al (Scand. J. Surg., 92-57-64, 2003).

Claims 28 and 31-32 are further drawn to additionally administering an antineoplastic agent at the same time, before or after administration of the human antibody (see claims 31 and 32)

The references in the above 103(a) teach and suggest methods as set forth above. They do not expressly teach administering an antineoplastic agent to treat colon cancer. This deficiency is made up for by the teachings of Rao et al.

Rao et al teach that it is common to treat colon cancer with antineoplastic chemotherapy agents such as 5FU (see entire document, e.g., abstract and page 63).

Accordingly, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to have further administered 5FU at the same time, before or after administration of the human antibody in order to treat colon cancer.

Notably, as both the claimed antibody and 5FU were known in the art to be effective for the same purpose, i.e., inhibiting and/or killing colon cancer cell, one of skill in the art would have been motivated to use both to treat colon cancer to provide more effective treatment. Furthermore, as both were known in the art to inhibit and/or kill colon cancer cells one of skill in the art would have expected success in practicing such methods.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Conclusion

10. No claim is allowed.

11. Applicant's amendment necessitated the new ground(s) of rejection presented in

this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

12. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Strober et al (US Patent 5,853,697, 1998, of record) teach that when administering antibodies to a human that one skilled in the art realizes that dosages are best optimized by the practicing physician and methods for determining dosages are described in the art (see column 3). Tokuda et al (BJC 8:1419-1425, 1999, of record) teach that antibody pharmacokinetic simulations used to establish dose schedules for therapeutic antibodies, predetermined serum trough levels and dose schedules for the respective next administration to maintain a minimum serum trough level of antibody are known in the art.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brad Duffy whose telephone number is (571) 272-9935. The examiner can normally be reached on Monday through Thursday, 6:15 AM to 4:45 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Misook Yu can be reached on (571) 272-0839. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Respectfully,
Brad Duffy
571-272-9935

/bd/
Examiner, Art Unit 1643
February 22, 2012

/Misook Yu/
Supervisory Patent Examiner, Art Unit 1642